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09/913,762	11/27/2001	Graeme Milligan	9013-13	5290

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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
913762	MILLIGAN et al
Examiner	**Group Art Unit**
SAUNDERS	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 9/2/03.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-29, 32 is/are pending in the application.

Of the above claim(s) 27-29, 32 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Amendment filed 9/02/03 has been entered.

Claims 1-29 and 32 are pending.

Claims 1-26 of Group I are under examination.

Applicant's election without traverse of I in Paper No. filed 9/2/03 is acknowledged.

Applicant's election of species for the reporter protein being luciferase and for the receptor protein being G-coupled is acknowledged. The examiner does not consider instant claims 16-17(limited to a green fluorescent protein reporter) as reading on the elected species of reporter. However, claims limited to non-elected species will be examined on the merits, to the extent that prior art has been submitted by applicant or that prior art is otherwise found by the examiner.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

The disclosure is objected to because of the following informalities: The examiner finds the disclosure confusing and contradictory; at page 31 line 24 it is considered that recitation of "agonist ligand" should read as ---antagonist/inverse agoinst ligand—in order to be consistent with the disclosure at page 27, line 15-page 28, line 4.

It is also considered that at page 31, line 26 "antagonist/inverse agonist ligands" should read as—agonist ligands—in order to be consistent with the disclosure at page 30, line 26-page 31, line 5. Clarification is requested.

Appropriate correction is required.

At page 31, line 5, --microplate--has been misspelled.

Also with respect to the specification, the examiner notes that sequences are recited at pages 20-21, 32-33, 39, and 43-44 and 48 without SEQ ID NOS for their identification; full compliance with 37 CFR 1.821-1.825 is required in the next response.

Claim 17 is objected to because of the following informalities: in claim 17--fluorimetry--has been misspelled. Appropriate correction is required.

Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is incomplete and fails to show the functional, cooperative relationship between the recited components. Firstly it is not clear as to the relationship between the compound and the membrane receptor/reporter fusion protein. Does the compound interact with the receptor or with the reporter segment of the fusion protein? Secondly, it is not clear what is detected in step 6). Is a signal from the reporter segment of the fusion protein detected?

Claim 6 is unclear as to how " or can in themselves disrupt such interactions" is distinguished from what is previously recited.

Claim 8 is unclear by reciting "or therapy" because no therapeutic administration step is recited.

In claims 4-5 "activity" is unclear. Is this the activity of the receptor or of the reporter portion of the fusion protein?

In claims 14-16 and 18-20 "said reporter protein" lacks antecedent basis because the only protein previously recited is a "receptor/reporter protein".

In claim 12 "binding" is unclear because it is not clear if the compound binds to the receptor or to the reporter segment of the fusion protein.

In claim 15 "functionality" is unclear. Is this a reference to the function of the receptor or of the reporter portion of the fusion protein?

In claims 22-23, "or the like" and "such as" are indefinite.

Claim 24 is unclear by using inconsistent terminology. The preamble recites simply "compound" while steps c) and d) recite "test compound". Consistency is required.

In claim 24, step d) "the reporter protein" and "the membrane complex" each antecedent basis.

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 3 fails to limit base claim 2, since any receptor must inherently be either wild type or mutant (whether a naturally occurring mutation or an engineered mutation).

Claims 7-8 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7 does not limit base claim 1 because any compound which is detected according to claim 1 would

inherently be one of an "inverse agonist, antagonist, or agonist". Claim 8 fails to further limit because "study of receptor function or therapy" encompasses all possible uses.

Prior to examination over the prior art the effective filing date of the instant claims must be established. Priority document GB 9903767.3 is considered to support the instant claims. Thus the effective filing date is 2/18/99. Thus McLean et al (document D4 cited by IPEA) published in 12/99 is not cited as prior art. Likewise, Siegel et al (WO 98/30715, document D4 cited by the IPEA) is not cited; however, note citation of US 6,660,844 further infra.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 8-10, 13-17, 20-22 and 24 are rejected under 35 U.S.C. 102(b) as being entirely anticipated by Barak et al (molec. Pharmacol. 2, 177, 1997).

Barak et al show cells transfected with an expression vector for a beta-2 andrenergic receptor green fluorescent protein fusion construct. Barak et al treat such cells with various agonists and antagonists of the receptor and then observe cellular distribution of fluorescence due to the GFP portion of the fusion protein. This is all that

is required to anticipate claim 1, since a "compound" can be any known antagonist or agonist, dependent claims 9, 13 and 16 are also clearly anticipated.

With respect to claim 24, this is deemed anticipated since the term "test compound" adds no weight over the term "compound". Also step b) is properly considered shown, since Barak et al determined initial, or time zero, cellular distribution of GFP fluorescence. Step d) is shown since Barak et al determined subsequent changes in the cellular distribution of GFP fluorescence.

Dependent claim 8 is anticipated because Barak et al use agonists and antagonists to study the function of the fused receptor.

Claim 10 is anticipated since Barak et al use a wild type receptor (page 178, col. 2).

Regarding claim 14, note Fig. 1 and page 178 col. 2.

For claim 15, note abstract; page 179, col.2 and page 181, col.1.

Regarding claim 17, note fluorescence microscopy taught at page 181.

With respect to claims 20-22, the fluorescence studies at page 181 employ fluorescence of GFP to localize the cellular distribution of the fused receptor in plated cells.

Claims 1-3, 6-9, 13-17, 20 and 24 are rejected under 35 U.S.C. 102(e) as being entirely anticipated by Siegel et al (6,660,844).

Siegel et al has an equivalent disclosure to WO 98/30715, cited on form 1449. The US patent has an effective 102(e) date of 1/7/97.

Siegel et al teach expression of fusion proteins of a responsive polypeptide linked to a GFP polypeptide. Responsive polypeptides include cell membrane receptors, such as G-protein coupled receptors. See col. 5, lines 7+. They teach that cells can be transfected to express such fusion proteins and then uses to screen for the activity of test compounds that bind to the responsive polypeptide, by means of determining changes in the fluorescent properties of GFP. See col.2, lines 34-45 and col.15, lines 42-58. From these teachings, claims 1-3, 7-9 and 16 are anticipated.

Regarding claim 6, it is taken from the broadest reasonable interpretation that any compound "that disrupts normal membrane interactions" would be one that "alters the activity" (Siegel at col. 15, lines 42-43) of a membrane receptor expressed as a fusion protein in a cell for screening assays.

Claim 13 is rejected, since Siegel et al teach receptors for opioids (col. 5, line 65).

Claim 14 is rejected because Siegel et al teach 5' to 3' fusion of a membrane ion channel protein encoding DNA to a GFP encoding DNA. See example 1 and fig. 1.

Regarding claim 15, note col.4 lines 3-4 and example 2.

With respect to claim 17, note example 2. Regarding claim 20, note col.19, lines 28-30.

With respect to claim 24, note that col. 2, lines 38-40 teach measuring the optical (fluorescent) activity of the expressed fusion protein "before and after the cell signaling event." This is sufficient to anticipate the steps of claim 24. Even though Siegel et al

teach that one would compare this signaling event to that obtained with a standard sample, the use of such a standard sample is permitted by the open nature of claim 24.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9-12, and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barak et al in view of Leurs et al (TIBS, 23 418 1998).

Barak et al have been cited supra, under 102, against base claims 1, 9-10, 24.

Presently Leurs et al are cited for showing that, when an inverse agonist binds to a constitutively active mutant form of a GPCR, there is an upregulation in the amount of the GPCR on the cell membrane, due to a "stabilization of the inactive GPCR conformation with inverse agonists" such that these "inverse agonists will subsequently prevent constitutive R* dependent downregulation, which will be seen as an inverse agonist upregulation." This mechanism is consistent with what is recited in instant claims 11-12 and 24. Note section spanning pages 420-421 of Leurs et al. Leurs et al also teach that an agonist binding to wild type receptor can downregulate receptor density. This is consistent with claim 25 see page 421, col.1.

Since Barak et al's assay using the GPCR –GFP fusion protein measures the amount of GFP reporter activity at the cell membrane, one would have fully expected that when an inverse agonist upregulates the density of receptor at the cell membrane, as taught by Leurs et al, there would be an increase in the degree of GFP receptor

activity, as recited in claims 12 and 26. Likewise one would have expected that when an agonist downregulates the density of receptor at the cell membrane, as taught by Leurs et al, there would be a decrease in the degree of GFP reporter activity, as recited in claim 25.

Claims 1-5, 9-12 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al in view of Leurs et al and Barak et al.

Siegel et al have been cited supra under 102 against base claims 1-2, 9-10 and 24.

Leurs et al have also been noted supra for teaching that an inverse agonist can upregulate expression of a CAM~GPCR and that an agonist can down regulate membrane expression of a wild type GPCR.

It has also been noted supra that Barak et al teach that a GPCR-GFP fusion protein provides a reporter signal at the cell membrane and thus, when considered with the teachings of Leurs et al, one would have expected inverse agonists and agonists to have the effects upon the reporter signal that are recited in instant claims 11-12 and 25-26.

Further, when screening for compounds having an effect on membrane receptor function, according to the method of claim 2, as taught by Siegel et al, one would have likewise expected that inverse agonists and agonists would effect the reporter signal changes recited in instant claims 3-5.

Claims 1-2, 13-14, 18-19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barak et al in view of Bryan et al (6,232,107).

Bryan et al has a 102(e) date of 3/27/98.

Barak et al have been cited supra against base claim 1. They do not teach or suggest use of a fusion protein, in which the reporter segment is luciferase from Renilla reniformis. Bryan et al are relied upon for teaching the use of numerous luciferases, including those derived from R. reniformis, as being suitable for use as reporter segments in fusion proteins. See col. 6, line 30-col. 8, line 51; col. 34, line 29-col. 35, line 45. They also teach, as do Barak et al, that one may use cells transformed with fusion proteins containing a GFP reporter see col.14, lines 20-48. They also teach that fusion proteins with reporters may include cell membrane receptors, including opiate receptors (which is a GPCR as in claims 13-14) for use in screening. See col.26, lines 15-67; col.28, lines 12-48.

Throughout their disclosure, Bryan et al teach that luciferase reporters and GFP reporters may be used interchangeably. Thus it would have been obvious that any screening method taught by Barak et al employing GFP as the reporter would also be capable of being accomplished with any luciferase taught by Bryan et al as the reporter.

Regarding the microplate/multiwell plate limitations of instant claims 19 and 23 note Bryan et al at col.7, lines 40-50.

Claims 1-2, 13-14, 18-19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al in view of Bryan et al.

Siegel et al have been cited supra against base claim 1. They do not teach or suggest use of a fusion protein in which the reporter segment is luciferase from Renilla reniformis. From the teachings of Bryan et al, also noted supra, it would have been

obvious to conduct the screening assays of Siegel et al with the use of luciferase in lieu of GFP as the reporter segment of receptor-reporter fusion proteins.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is (703) 308-3976. The examiner can normally be reached on Monday-Thursday 8 am - 5:30 pm. Alternative Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding are assigned are (703) 308-4242 and (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Saunders/tgd

January 6, 2004

David A Saunders
DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1614